ANIMAL MODEL OF HUMAN DISEASE

# *Acute and Chronic Viral Myocarditis*

## *Acute Diffuse Nonsuppurative Myocarditis and Residual Myocardial Scarring Following Infection With Canine Parvovirus*

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CANINE PARVOVIRUS (CPV) suddenly emerged in the 1970s worldwide as the cause of a new disease complex of dogs. The disease occurs in three distinct forms: 1) leukopenia, vomiting, and diarrhea in dogs from about 8 weeks of age (similar to panleukopenia—a well recognized parvovirus disease in cats); 2) nonsuppurative myocarditis and death from heart failure in pups 3–8 weeks old; and 3) generalized disease with focal necrosis of many tissues in pups less than 2 weeks old.[1]

Although parvoviruses have not been confirmed as pathogens of man, canine parvovirus myocarditis (CPVM) could be a useful model for the study of acute-onset and chronic-progressive cardiomyopathies of man.

### Biologic Features

Parvoviruses are single-stranded DNA viruses which require actively dividing (cycling) cells for their replication. Specifically, parvoviruses require cells in the late DNA synthesis phase of the cell cycle.[2,3] While the postnatal myocardium is not normally regarded as a tissue with a high rate of cell replication, autoradiographic studies in pups 1–45 days old confirmed that a significant proportion of cardiac myocytes synthesized DNA during the first two weeks of life,[4] indicating their potential suitability as targets for parvovirus infection.

Most natural CPV infections are subclinical; however, CPVM can result in the loss of complete litters of pups. Death from acute CPVM is sudden, usually without premonitory signs. Dyspnea and electrocardiographic (ECG) abnormalities have been reported occasionally, although ECG changes are not consistently present.[5] Some members of affected litters survive the acute phase to subsequently succumb to chronic cardiac disease.[6]

Both acute and chronic myocarditis can be experimentally produced in pups following *in utero* inoculation of canine fetuses 8 days before parturition.[5] The experimental disease appears similar to that seen naturally. Experiments in our laboratory demonstrated that 2 of 4 pups inoculated *in utero* died suddenly, 23 and 27 days after inoculation. Two pups remained clinically normal until euthanasia was performed at 87 and 131 days after inoculation. The 2 pups that died acutely had a dilated heart with irregular areas of pallor visible on the epicardial surface. In 2 pups euthanized at 87 and 131 days the heart also was dilated, but the epicardial surface was covered with focal, opalescent, depressed lesions (Figure 1). These foci extended into the myocardium, sometimes to the endocardium.

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Histologically, in acute CPVM disease there is a mild, diffuse, mainly lymphocytic infiltration throughout the heart, with interstitial edema and limited myocardial degeneration. Characteristic parvovirus intranuclear inclusions are present in cardiac myocytes with the acute disease (Figure 2). There also are dense focal aggregates of lymphocytes which displace myocardial cells (Figure 3).

There is little evidence of direct CPV-induced cell necrosis, and inclusions are found among a large proportion of uninfected, apparently normal myocytes. As suggested by Figure 2 and from *in vitro* data,[7] parvoviruses are not highly lytic agents. The persistence of the inclusion-bearing myocytes may provide a focus of foreign antigen and provoke the inflammatory response observed. Death from heart failure has been attributed to an immunologic response to sporadically infected myocytes (ie, those cells which had entered the DNA synthesis phase of the cell cycle), giving rise to foci of irritation that have interfered with normal conduction. The importance of immunologic phenomena in the pathogenesis of both acute and chronic CPVM is also suggested by the delay between infection and overt natural or experimental disease, and by the nature of the inflammatory response.

In the chronic form of CPVM there are large foci of myocardial fibrosis, with isolated myocytes and infiltrating lymphocytes and plasma cells in fibrotic areas. Contraction of scar tissue (Figure 4) causes the irregularities seen grossly in the epicardium (Figure 1). The focal nature of the lesions is best appreciated in the chronic disease, and suggests local, limited virus replication after initial infection. However, the progressive nature of CPVM is indicated by interstitial edema present around fibrotic foci and smooth muscle hypertrophy of blood vessel walls in the heart. Experimentally infected pups that survive the acute phase of CPVM may die from chronic sequellae, such as fibrous scars in the heart that contract to cause valvular insufficiency, compromise conduction pathways, or restrict blood flow to areas of the myocardium.

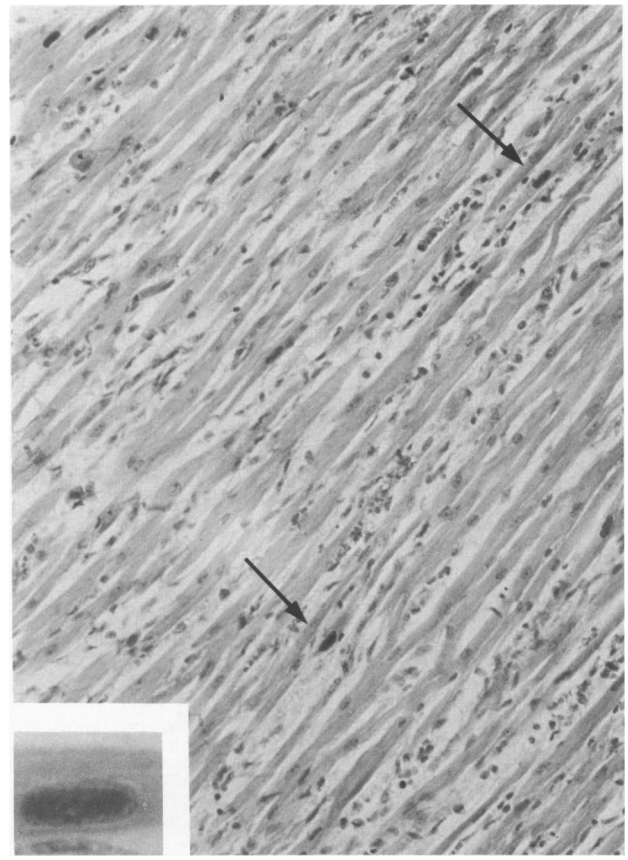

**Figure 2**—Acute canine parvovirus myocarditis with interstitial edema and a diffuse, mainly lymphocytic, infiltration through the myocardium. Typical intranuclear inclusion bodies (*arrows*) are present in cardiac myocytes. (H&E, ×200) **Inset**—The intranuclear inclusion in the myocyte fills the nucleus except for a narrow margin at the nuclear membrane. (H&E, ×1200)

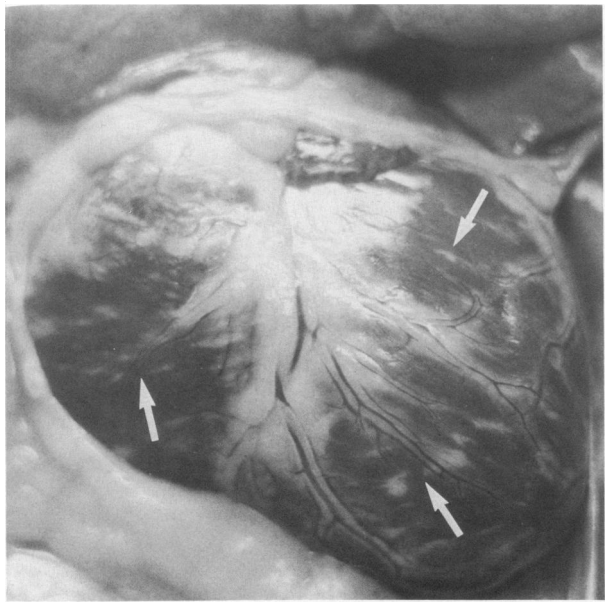

**Figure 1**—Heart *in situ* from a pup examined 131 days after infection with canine parvovirus. Foci or streaks of fibrosis (*arrows*), visible from the epicardial surface, extend through the full thickness of the myocardium.

## Comparison With Human Disease

Coxsackie B virus infection is the most common cause of viral myocarditis of man.[8,9] Acute viral myopericarditis is regarded as an important cause of dilated (congestive) cardiomyopathies,[10] and some chronic idiopathic cardiomyopathies may also be of

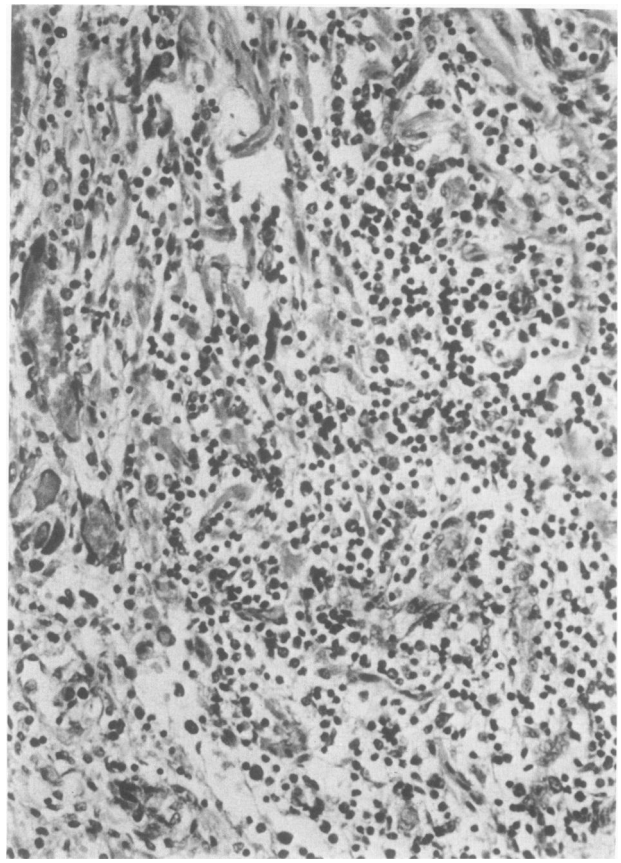

**Figure 3**—Acute canine parvovirus myocarditis with an intense infiltration of lymphocytes disrupting myocardial fibers. (H&E, ×240)

viral origin.[11] The greatest danger from acute viral myocarditis for man, lies in arrythmia.[12] Congestive cardiomyopathy, possibly in association with immunologic damage to myocardium, may also occur.[13] It has been suggested that extensive focal fibrosis seen in cases of idiopathic cardiac hypertrophy may relate to remote past infection. If sufficiently severe, any cause of focal myocardial degeneration could lead to death from congestive heart failure.[14] ECG changes often are nonspecific and insufficient to confirm a diagnosis of myocarditis when other clinical signs are absent.[15]

Millions of people in Central and South America suffer from chronic cardiomyopathy subsequent to infection with *Trypanosoma cruzi* (Chagas' disease). ECG abnormalities and heart failure with multifocal scarring occur. No specific treatment exists. Immunologic mechanisms are postulated as important in the chronic phase of this disease.[10]

The similarity of acute or chronic CPVM to various types of cardiac disease of man indicates that this canine disease may be a potentially useful model for studies on clinical progress and responses to treatment for human cardiomyopathies.

## Availability

Naturally occurring CPVM is now comparatively uncommon. Most bitches have been exposed to infection, or vaccinated, so that maternal antibody present in their colostrum is transferred to and protects pups during the critical first few weeks of postnatal development, when productive myocardial infection with CPV is possible. Antibody transfer in dogs is mainly via colostrum[16]; thus colostrum-deprived pups even from seropositive dams would be susceptible to infection from birth, although direct *in utero* inoculation of fetuses may prove a more reliable method for producing this disease. There is, however, no evidence that natural infection is acquired *in utero*. Because of the ubiquitous nature of the virus and its extreme resistance to physical and chemical disinfection, experimental pups would need to be maintained under specific pathogen-free conditions.

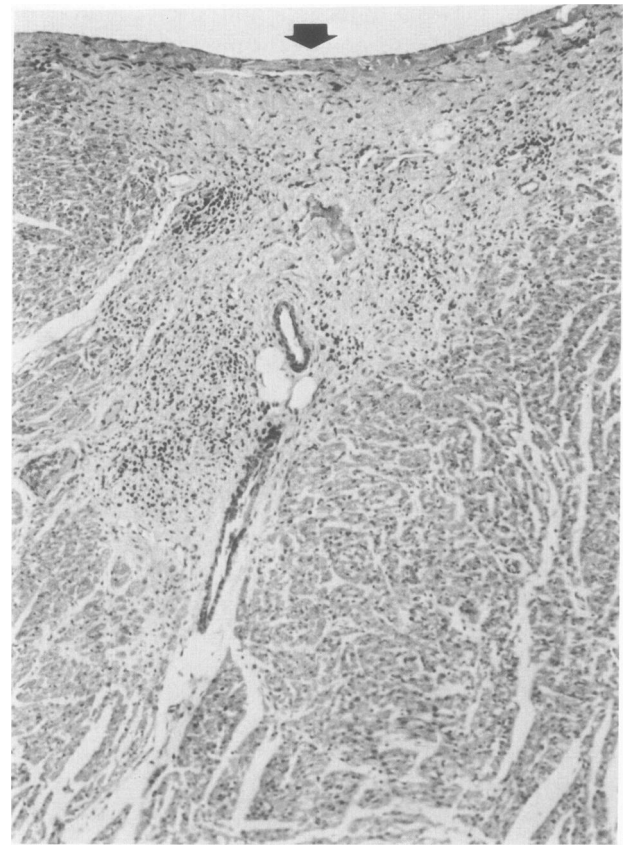

**Figure 4**—Chronic canine parvovirus myocarditis with a focus of fibrosis in the myocardium and a depression in the epicardial surface (*arrow*) caused by contraction of scar tissue. Notice infiltrating lymphocytes and plasma cells and isolated myocytes at the periphery of the fibrous tissue. (H&E, ×100)

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